



Invited Commentary | Neurology

Long-term Risk of Cognitive Impairment and Dementia Following Bilateral Oophorectomy in Premenopausal Women—Time to Rethink Policies?

Marios K. Georgakis, MD, PhD; Eleni T. Petridou, MD, PhD

Highly prevalent in the aging population, cognitive impairment and dementia represent major causes of disability, dependency, and death worldwide. Lack of effective treatments has shifted interest to identification of modifiable risk factors and developments of preventive strategies. Accumulating evidence suggests that earlier menopausal transition may accelerate biological aging among women¹ and subsequently contribute to a higher risk of late-life multimorbidity including cognitive decline.^{2,3} This has raised the hypothesis that surgical removal of ovaries in premenopausal women might lead to long-term health consequences that have been underestimated. Indeed, a series of studies during the last 2 decades have shown that bilateral oophorectomy at 45 years of age or earlier is associated with higher risk of cognitive impairment and dementia.⁴ These studies, however, had clear limitations: (1) no access to data about menopausal status at the time of the surgery; (2) grouping into the same risk category of all women with surgically induced menopause (notably oophorectomy but also hysterectomy without oophorectomy, which does not lead to a premature cessation of exposure to ovarian hormones); (3) too short intervals between surgery and cognitive assessments to examine late-life outcomes; and (4) no access to data on indication of bilateral oophorectomy, thus not allowing to examine the need for surgery.

Against this background, the population-based linkage study by Rocca et al⁵ published in *JAMA Network Open*, aims to address the same question by overcoming major limitations of previous studies. The authors leveraged data from 2732 women aged 50 to 89 years who were randomly sampled through a medical records-linkage system in Olmsted County, Minnesota. The study participants underwent detailed neuropsychological testing covering memory, attention/executive function, visuospatial ability, and language approximately 30 years after the surgery. The authors retrospectively extracted information from the medical records of the study participants on history of bilateral oophorectomy, age and menopausal status at the time of surgery, surgical indication, details about the surgery, and use of estrogen therapy after the oophorectomy. Following adjustments for age, education, and APOE genotype, the authors found that women who underwent bilateral oophorectomy before menopause and before age 46 years had higher odds for clinically diagnosed mild cognitive impairments (OR, 2.21; 95% CI, 1.41-3.45), as compared with women who did not undergo bilateral oophorectomy. Furthermore, these women scored lower in a composite score of global cognitive performance and in the domain of attention/executive function. Bilateral oophorectomy performed after natural menopause or before natural menopause but after the age of 45 years was not associated with cognitive impairment. In exploratory and relatively underpowered subgroup analyses, the authors found this association to be significant also for benign indications of bilateral oophorectomy and to be of similar magnitude for both women who received or did not receive estrogen therapy following the surgery.

The study by Rocca and colleagues⁵ contributes valuable new data to a major public health importance issue and addresses a number of important shortcomings of existing literature. Information on menopausal status at the time of the surgery and the exact procedure reduced misclassification of the exposure of interest. Furthermore, data on indication of bilateral oophorectomy allowed exploring unique insights about whether the higher risk associated with bilateral oophorectomy could be potentially preventable. Although the analyses were underpowered, the findings support an association between mild cognitive impairment and women

+ Related article

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

who underwent bilateral oophorectomy for benign indications, such as adnexal masses, cysts, or endometriosis. This is important, because in many of those cases, removal of both ovaries could be avoided. Finally, data on the associations with specific cognitive domains over and beyond a global composite score, the analyses enabled the development of hypotheses regarding potential conditions underlying the observed associations that have been linked with specific patterns of cognitive impairment.

Some important methodological limitations should be considered, related mainly to tentative selection bias underpinning the associations derived from this study. In fact, only women who survived to this old age were recruited to the study, whereas women who died early after bilateral oophorectomy have been excluded. This selection on survival might introduce collider bias, since both bilateral oophorectomy and cognitive impairment could affect mortality. Second, the study was underpowered to explore the risk of cognitive impairment associated with more younger ages at bilateral oophorectomy, such as before the age of 40, where the effect would be expected to be even larger. Third, there were no serial assessments of cognitive performance to allow exploration of associations with cognitive decline. Fourth, the sample is restricted to White women living in the specific setting of Olmsted County, Minnesota, and might thus not be representative of other populations with different socioeconomic, racial, or ethnic characteristics.

Bilateral oophorectomy is a procedure commonly performed in women for benign medical conditions. At least until the beginning of the 21st century, it was a standard practice to perform the procedure alongside hysterectomy for any indication as a prophylactic measure against ovarian cancer.⁶ A series of observational studies have provided consistent evidence that bilateral oophorectomy when performed at an early age in still premenopausal women is associated with lower risk of ovarian and breast cancer. In contrast, a higher all-cause mortality and higher risk for dementia, depression, parkinsonism, cardiovascular disease, and nonovarian/nonbreast cancers has been reported.³ As bilateral oophorectomy is still a common procedure at least in the well-resourced countries, the results of these studies should alert clinicians about its potential public health consequences.⁶ Given that the abrupt cessation of ovarian hormones might be accompanied by previously underestimated long-term adverse effects, treating physicians proposing the operation should weigh its benefits against potential long-term harmful effects, especially among women without an absolute indication.

A key open question is why and how bilateral oophorectomy promotes cognitive aging. The prevailing hypothesis is that the abrupt endocrine cessation of exposure to ovarian hormones accelerates the aging process. DNA methylation data from human blood, saliva, and buccal epithelium suggest that an earlier menopausal transition is associated with an epigenetic signature of aging.¹ This is further supported by epidemiological evidence about a higher all-cause mortality among premenopausal women undergoing removal of all ovarian tissue vs those conserving ovarian tissue at time of hysterectomy for benign disease.⁷ Possible downstream mediators of this association merit consideration. Accelerated aging may contribute to cognitive decline by inducing atherosclerotic stroke, arteriosclerosis in small vessels, and also accumulation of Alzheimer neuropathology. This study provided evidence for a specific association with impairment in attention and executive function, domains more commonly affected by vascular pathologies, as compared to Alzheimer disease.

In conclusion, the study by Rocca et al⁵ adds to the existing literature regarding long-term cognitive consequences of bilateral oophorectomy in young premenopausal women; however, several issues remain to be addressed and should motivate future research. Large-scale prospectively designed general population-based studies are needed to remove bias, reliably quantify risks associated with bilateral oophorectomy, and accurately estimate the absolute contribution to cognitive impairment and dementia. Estimates of the number needed to harm would enable weighing the long-term risk against the benefits of the procedure in specific groups of women, such as carriers of high-risk *BRCA1* or *BRCA2* variants. Most important from a clinical perspective is whether these women would benefit from specific hormone replacement therapy

schemes. Observational studies cannot reliably answer this question, and possibly it is time to rethink designing trials in specific groups of women who underwent bilateral oophorectomy before 46 years of age starting treatment immediately thereafter. Finally, observational studies should explore associations with endophenotypes of cognitive decline, such as neuroimaging markers of small vessel disease or burden of tau-associated or amyloid-associated pathologies that could provide insights about the underlying mechanisms. Such insights could guide the development of focused preventive strategies for ameliorating the long-term risk of cognitive impairment among these women.

ARTICLE INFORMATION

Published: November 11, 2021. doi:[10.1001/jamanetworkopen.2021.33016](https://doi.org/10.1001/jamanetworkopen.2021.33016)

Open Access: This is an open access article distributed under the terms of the [CC-BY License](#). © 2021 Georgakis MK et al. *JAMA Network Open*.

Corresponding Author: Marios K. Georgakis, MD, PhD, Center for Genomic Medicine, Massachusetts General Hospital, 185 Cambridge St, Boston, MA 02114 (marios.georgakis@med.uni-muenchen.de).

Author Affiliations: Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, Boston (Georgakis); Program of Medical and Population Health, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Georgakis); Institute for Stroke and Dementia Research, University Hospital of LMU Munich, Munich, Germany (Georgakis); Department of Hygiene Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece (Petridou).

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Levine ME, Lu AT, Chen BH, et al. Menopause accelerates biological aging. *Proc Natl Acad Sci U S A*. 2016;113(33):9327-9332. doi:[10.1073/pnas.1604558113](https://doi.org/10.1073/pnas.1604558113)
2. Georgakis MK, Kalogirou EI, Diamantaras AA, et al. Age at menopause and duration of reproductive period in association with dementia and cognitive function: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;73:224-243. doi:[10.1016/j.psyneuen.2016.08.003](https://doi.org/10.1016/j.psyneuen.2016.08.003)
3. Rocca WA, Mielke MM, Gazzuola Rocca L, Stewart EA. Premature or early bilateral oophorectomy: a 2021 update. *Climacteric*. 2021;24(5):466-473. doi:[10.1080/13697137.2021.1893686](https://doi.org/10.1080/13697137.2021.1893686)
4. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2019;106:9-19. doi:[10.1016/j.psyneuen.2019.03.013](https://doi.org/10.1016/j.psyneuen.2019.03.013)
5. Rocca WA, Lohse CM, Smith CY, Fields JA, Machulda MM, Mielke MM. Association of premenopausal bilateral oophorectomy with cognitive performance and risk of mild cognitive impairment. *JAMA Netw Open*. 2021;4(11):e2131448. doi:[10.1001/jamanetworkopen.2021.31448](https://doi.org/10.1001/jamanetworkopen.2021.31448)
6. Asante A, Whiteman MK, Kulkarni A, Cox S, Marchbanks PA, Jamieson DJ. Elective oophorectomy in the United States: trends and in-hospital complications, 1998-2006. *Obstet Gynecol*. 2010;116(5):1088-1095. doi:[10.1097/AOG.0b013e3181f5ec9d](https://doi.org/10.1097/AOG.0b013e3181f5ec9d)
7. Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ*. 2017;356:j372. doi:[10.1136/bmj.j372](https://doi.org/10.1136/bmj.j372)